Amendments to the Specification

Please amend the title of the application as follows:

COMPOSITIONS AND METHODS COMPRISING ~~PROTEIN~~ PROTEINASE ACTIVATED RECEPTOR ANTAGONISTS

At page 1, line 23, please delete the paragraph and substitute therefor the following:

The present invention relates to compositions and methods comprising ~~protein~~ proteinase activated receptor antagonists. More particularly, the present invention relates to the use of proteins, peptides and biomolecules that bind to ~~protein~~ proteinase activated receptors, and inhibit the processes associated with the activation of that receptor. More specifically, the present invention provides novel compositions and methods for the treatment of disorders and diseases such as those associated with abnormal cellular proliferation, angiogenesis, inflammation and cancer.

At page 4, line 31, please delete the paragraph and substitute therefor the following:

Recently studies have been conducted that correlate abnormal ~~protein~~ proteinase activated receptor activity with certain disorders and diseases. Of particular interest is ~~protein~~ proteinase activated receptor-2 which has been discovered to be associated with disorders such as inflammation, angiogenesis, and sepsis. Although several attempts have been made, no effective antagonists of ~~protein~~ proteinase activated receptors have been identified.

At page 5, line 3, please delete the paragraph and substitute therefor the following:

What is needed are compositions and methods that can inhibit abnormal or undesirable cellular function, especially functions that are

associated with undesirable cellular proliferation, angiogenesis, inflammation and cancer. The compositions should comprise proteins, peptides and biomolecules that overcome the activity of endogenous ~~protein~~ proteinase activated receptor ligands and prevent the activation of ~~protein~~ proteinase activated receptors thereby inhibiting the development of abnormal physiological states associated with inappropriate ~~protein~~ proteinase activated receptor activation. Finally, the compositions and methods for inhibiting ~~protein~~ proteinase activated receptor activation should preferably be non-toxic and produce few side effects.

At page 5, line 17, please delete the paragraph and substitute therefor the following:

Compositions and methods are provided that are effective in inhibiting abnormal or undesirable cell function, particularly cellular activity and proliferation related to angiogenesis, neovascularization, inflammation, tumor growth, sepsis, neurogenic and inflammatory pain, asthma and post operative ileus. The compositions comprise a naturally occurring or synthetic protein, peptide, protein fragment or biomolecule containing all, or an active portion of a ligand that binds ~~protein~~ proteinase activated receptors, optionally combined with a pharmaceutically acceptable carrier.

At page 5, line 27, please delete the paragraph and substitute therefor the following:

Representative ligands or antagonists useful for the present invention comprise proteins, peptides and biomolecules that bind ~~protein~~ proteinase activated receptors, such as, but not limited to, ~~protein~~ proteinase activated receptor 1 (PAR-1) or ~~protein~~ proteinase activated receptor 2 (PAR-2), ~~protein~~ proteinase activated receptor 3 (PAR-3), and ~~protein~~ proteinase activated receptor 4 (PAR-4). Preferred ligand compositions of the present invention, include, but are not limited to, proteins comprising LIGK (SEQ ID NO:1), LIGKV (SEQ ID NO:2), KGIL (SEQ ID NO:3), KGI (SEQ ID NO:4), AGI

(SEQ ID NO:5), IGA (SEQ ID NO:6), KGA (SEQ ID NO:7), KGA (SEQ ID NO:8), KAI (SEQ ID NO:9), IAK (SEQ ID NO:10), RGI (SEQ ID NO:11), IGR (SEQ ID NO:12), Dab-GI (Dab= diamino butanoic acid) (SEQ ID NO:13), Dap-GI (Dap= diamino proprionic acid) (SEQ ID NO:14), IG-Dab (SEQ ID NO:15), IG-Dap (SEQ ID NO:16), LIG-Dab (SEQ ID NO:17), Dab-GIL (SEQ ID NO:18), LIG-Dap (SEQ ID NO:19), Dap-GIL (SEQ ID NO:20), LIG-Orn (SEQ ID NO:21), Orn-GIL (SEQ ID NO:22), Orn-GI (SEQ ID NO:23) and IG-Orn (SEQ ID NO:24), ENMD 545 (Figure 1), ENMD 547 (Figure 1), and various peptidomimetic structures provided in Figure 2. Also contemplated within the scope of this invention are ligands and antagonists that comprise functional and structural derivatives and equivalents of the above-listed biomolecules.

At page 6, line 16, please delete the paragraph and substitute therefor the following:

Preferably, the protein, peptide, protein fragment or biomolecule contains all or an active portion of the above identified ligands and antagonists. The term "active portion", as used herein, means a portion of a protein, peptide or biomolecule that inhibits ~~protein~~ proteinase activated receptor activation. Also included in the present invention are homologs, peptides, or protein fragments, or combinations thereof of the above-identified ligands and antagonists, that inhibit ~~protein~~ proteinase activated receptor activity.

At page 6, line 25, please delete the paragraph and substitute therefor the following:

It is believed that by inhibiting ~~protein~~ proteinase activated receptor activity, the methods and compositions described herein are useful for inhibiting diseases and disorders associated with abnormal ~~protein~~ proteinase activated receptor activity. The methods provided herein for treating diseases and processes mediated by ~~protein~~ proteinase activated receptors, such as

inflammation and cancer, involve administering to a human or animal the composition described herein in a dosage sufficient to inhibit ~~protein~~ proteinase activated receptor activity, particularly PAR-2 activity. The methods are especially useful for treating or repressing the growth of tumors, particularly by inhibiting angiogenesis.

At page 7, line 3, please delete the paragraph and substitute therefor the following:

Accordingly, it is an object of the present invention to provide methods and compositions for treating diseases and processes that are mediated by abnormal or undesirable ~~protein~~ proteinase activated receptor activity.

At page 7, line 22, please delete the paragraph and substitute therefor the following:

Yet another object of the present invention is to provide methods and compositions comprising the use of proteins, peptides, biomolecules, active fragments and homologs thereof that inhibit ~~protein~~ proteinase activated receptor activity.

At page 7, line 27, please delete the paragraph and substitute therefor the following:

Another object of the present invention is to provide methods and compositions for treating diseases and processes that are mediated by angiogenesis by ~~administrating~~ administering antiangiogenic compounds comprising ligands that bind ~~protein~~ proteinase activated receptor activity.

At page 7, line 32, please delete the paragraph and substitute therefor the following:

It is a further object of the present invention to provide methods and compositions for treating diseases and processes that are mediated by abnormal ~~protein~~ proteinase activated receptor activity.

At page 8, line 1, please delete the paragraph and substitute therefor the following:

It is another object of the present invention to provide methods and compositions for diagnosing diseases and disorders by measuring abnormal ~~protein~~ proteinase activated receptor activity.

At page 8, line 5, please delete the paragraph and substitute therefor the following:

It is still another object of the present invention to provide compositions comprising ligands that bind ~~protein~~ proteinase activated receptors wherein the compositions further comprise pharmaceutically acceptable carriers.

At page 8, line 9, please delete the paragraph and substitute therefor the following:

Yet another object of the present invention is to provide methods and compositions comprising ligands that bind ~~protein~~ proteinase activated receptors wherein the compositions further comprise pharmaceutically acceptable carriers that may be administered intramuscularly, intravenously, transdermally, orally, or subcutaneously.

At page 19, line 14, please delete the paragraph and substitute therefor the following:

The term "active portion" is defined herein as the portion of a ligand or molecule necessary for inhibiting the activity of ~~protein~~ proteinase activated receptors. The active portion has the ability to inhibit ~~protein~~ proteinase activated receptors expression by *in vivo* or *in vitro* assays or other known techniques.

At page 20, line 24, please delete the paragraph and substitute therefor the following:

As used herein, the phrase ~~"protein~~ "proteinase activated receptor" is defined to encompass all ~~protein~~ proteinase activated receptors ~~(PARS)~~ (PARs), including, but not limited to, PAR-1, PAR-2, PAR-3 and PAR-4.

At page 24, line 13, please delete the paragraph and substitute therefor the following:

The inhibitory proteins and peptides of ~~protein~~ proteinase activated receptors of the present invention may be isolated from body fluids including, but not limited to, serum, urine, and ascites, or may be synthesized by chemical or biological methods, such as cell culture, recombinant gene expression, and peptide synthesis. Recombinant techniques include gene amplification from DNA sources using the polymerase chain reaction (PCR), and gene amplification from RNA sources using reverse transcriptase/PCR. Ligands of interest are extracted from body fluids by known protein extraction methods, particularly the method described by Novotny, W.F., *et al., J. Biol. Chem.* 264:18832-18837 (1989).

At page 26, line 7, please delete the paragraph and substitute therefor the following:

The naturally occurring or synthetic protein, peptide, or protein fragment, containing all or an active portion of a protein, peptide or biomolecule that may bind to a ~~protein~~ proteinase activated receptor can be prepared in a physiologically acceptable formulation, such as in a pharmaceutically acceptable carrier, using known techniques. For example, the protein, peptide, protein fragment or biomolecule is combined with a pharmaceutically acceptable excipient to form a therapeutic composition.

At page 27, line 31, please delete the paragraph and substitute therefor the following:

Further, the term "effective amount" refers to the amount of the composition which, when administered to a human or animal, inhibits ~~protein~~ proteinase activated receptor activity, particularly undesirable cell proliferation, causing a reduction in cancer or inhibition in the spread and

proliferation of cancer. The effective amount is readily determined by one of skill in the art following routine procedures.

At page 28, line 23, please delete the paragraph heading and substitute therefor the following:

Antibodies of ~~Protein~~ Proteinase Activated Receptor Antagonists